CLINICAL PRACTICE GUIDELINE

Helicobacter Pylori and Gastroduodenal Ulcer Disease

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SUMMARY

Background: Helicobacter pylori-associated diseases and gastroduodenal ulcer disease are common conditions of major clinical and economic importance. There is thus a need for a guideline that incorporates the scientific knowledge gained in recent years and that takes specific aspects of the situation in Germany into account with regard to epidemiology, resistance status, diagnostic evaluation, and treatment.

Methods: This level-S3 consensus guideline was developed in accordance with the recommendations of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF). It was commissioned by the German Association for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS) and prepared in cooperation with other scientific societies. After search terms were compiled, a systematic, IT-supported literature search was performed in the PubMed and Cochrane databases. The search was restricted to articles that appeared in German or English from 2000 onward.

Results: H. pylori infection can be accurately diagnosed either non-invasively (with a ^{13}C-urea breath test or a stool antigen test) or invasively (with a rapid urease test, by histology, or by culture). Gastric and duodenal ulcer and gastric MALT lymphoma are absolute indications for eradication therapy; relative indications include functional dyspepsia, the prevention of gastric cancer in persons at risk, the initiation of long-term treatment with non-steroidal anti-inflammatory drugs (NSAID), and the prior occurrence of gastroduodenal complications with the use of either NSAID or acetylsalicylic acid (ASA). First-line therapy consists of a proton-pump inhibitor (PPI) and clarithromycin combined with either metronidazole or amoxicillin, given for at least one week.

Conclusion: This guideline enables the structured, evidence-based diagnosis and treatment of H. pylori infection and associated conditions, as well as of gastroduodenal ulcer disease.

Key words: Helicobacter pylori, gastric ulcer, duodenal ulcer, guideline

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After the (re)discovery of *Helicobacter pylori (H. pylori)* in 1983 by Warren und Marshall (1), the importance of this organism in gastroduodenal ulcer disease was recognized. In the years that followed, it was also found to play an etiological and pathogenetic role in gastric carcinoma and MALT lymphoma, and to be associated with yet other diseases of the stomach and other organs.

In view of the high frequency of *H. pylori* associated diseases, including gastroduodenal ulcer disease, and their major clinical and socioeconomic importance, an interdisciplinary guideline is needed that will take into account new scientific knowledge on this topic as well as specific considerations for Germany with respect to epidemiology, antibiotic resistance, diagnosis, and treatment. This guideline was developed on the initiative of the German Society for Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten*, DGVS) and in collaboration with other medical societies. It meets the methodological criteria for an evidence-based guideline of level 3 (S3) as defined by the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF).

In this brief summary, important practical aspects of the epidemiology, diagnostic evaluation, and treatment of *H. pylori* infection are presented, and the indications for its eradication are presented as recommended in the guideline. For further information, the reader is directed to the complete guideline (2), which also contains literature references for some pieces of information whose source is not specified in this article.

Methods

The organizing committee assembled the expert groups, named the group leaders, and defined seven groups of topics *(Box)*:

- Epidemiology
- Diagnostic evaluation, characterization, resistance, and resistance testing
- Indications for the treatment of *H. pylori* infection in benign disease
- Prevention and treatment of neoplastic diseases of the stomach (marginal zone B-cell lymphoma of MALT type, gastric carcinoma)
- Treatment of *H. pylori* infection

BOX

Guideline development group

- Guideline directors / organizing committee
  - Prof. Dr. W. Fischbach, Aschaffenburg
  - Prof. Dr. P. Malfertheiner, Magdeburg
- Topic group I:
  Epidemiology
  - Prof. Dr. W. E. Schmidt, Bochum (group leader)
  - Dr. O. Götze, Bochum (literature search)
- Topic group II:
  Diagnostic evaluation, characterization, resistance, and resistance testing
  - Prof. Dr. M. Kist, Freiburg (group leader)
  - PD Dr. U. Peitz, Münster (group leader)
  - PD Dr. A. Timmer, Freiburg (literature search)
- Topic group III:
  Indications for the treatment of H. pylori infection in benign disease
  - Prof. Dr. P. Layer, Hamburg (group leader)
  - Dr. U. Rosien, Hamburg (literature search)
- Topic group IV:
  Prevention and treatment of neoplastic diseases of the stomach (marginal zone B-cell lymphoma of MALT type, gastric carcinoma)
  - PD Dr. A. Morgner, Dresden (group leader)
  - PD Dr. M. Vieth, Bayreuth (group leader)
  - Dr. R. Schmelz, Dresden (literature search)
  - Dr. J. Bornschein, Magdeburg (literature search)
- Topic group V:
  Treatment of H. pylori infection
  - Prof. Dr. J. Labenz, Siegen (group leader)
  - PD Dr. G. Treiber, Homburg/Saar (group leader)
  - Dr. J. Maubach, Siegen (literature search)
- Topic group VI:
  Special considerations of H. pylori infection in children and adolescents
  - Prof. Dr. S. Koletzko, Munich (group leader)
  - Dr. A. Schwarzer, Munich (literature search)
- Topic group VII:
  Gastroduodenal ulcer diseases that are not associated with H. pylori
  - PD Dr. J. Hoffmann, Ludwigshafen (group leader)
  - Prof. Dr. C. Prinz, Munich (group leader)
  - Dr. J. Preiß, Berlin (literature search)

- Special considerations of *H. pylori* infection in children and adolescents
- Gastroduodenal ulcer diseases that are not associated with *H. pylori.*

A working group was established at the Charité Hospital (Berlin) in the framework of the competence network on chronic inflammatory bowel diseases (members: W. Höhne, J. Hoffmann, J. Preiß). The members of this working group conducted a workshop in which they instructed the participants in the working groups for each of the topics listed above in the proper procedures for choosing search terms and for performing formal literature searches. The searches were carried out in the PubMed and Cochrane databases. They were restricted to publications in English or German that had appeared from 2000 onward (guidelines, systematic reviews, randomized controlled trials, and observational studies). Computer specialists were available to help with the generation of consensus-supported dictionaries. The literature search on the chosen terms yielded nearly 20 000 articles. The flowchart in *Figure 1* shows, by way of illustration, the method that was used to select articles for evaluation in topic group I, "epidemiology."

Literature searching and supplementation finally yielded 490 selected articles, on the basis of which the group leaders formulated the questions to be addressed. These were then answered in the individual working groups, whereupon the final catalogue of questions was made accessible over the Internet for further processing by all guideline participants (Delphi technique). The group leaders made recommendations for consensus formation on the basis of the answers that had been received to the catalogue of questions, and these recommendations were discussed and revised in the individual working groups on the first day of the concluding consensus conference. Thereafter, the consensus recommendations were submitted to a vote via TED (Tele-Dialog, a tele-voting procedure) (*Table 1*). In general, the strength of the evidence determined the recommendation grade *(Table 2)*. In some cases where it was thought to be appropriate, however, the consensus conference chose to make the recommendation grade either higher or lower than the strength of the evidence alone might have implied.

Epidemiological situation in Germany

The Gram-negative bacterium *H. pylori* is an obligate pathogen that colonizes the gastric mucosa and induces a chronic, active type B gastritis. Conditions that can then arise in the affected tissue include gastroduodenal ulcer disease, distal (non-cardiac) gastric carcinoma, and marginal zone B-cell lymphoma of MALT (mucosa-associated lymphoid tissue) type (A, strong consensus) (6, 7).

The epidemiological situation in Germany is characterized by the following:

- An increasing rate of infection with age: 5% of children and 30% of adults are infected with *H. pylori* (3, 4)

- A markedly higher infection rate in immigrants (36% to 86%)
- A decline in infection rates in recent decades, and also projected into the future ([5]; cohort effect)
- Acquisition of the infection from family members during infancy
- Oral-oral, gastric-oral, and fecal-oral transmission
- Rare recurrent infections in adults (1% per year).

Vaccination or other preventive measures against *H. pylori* infection are currently unavailable.

Diagnosis of H. pylori infection

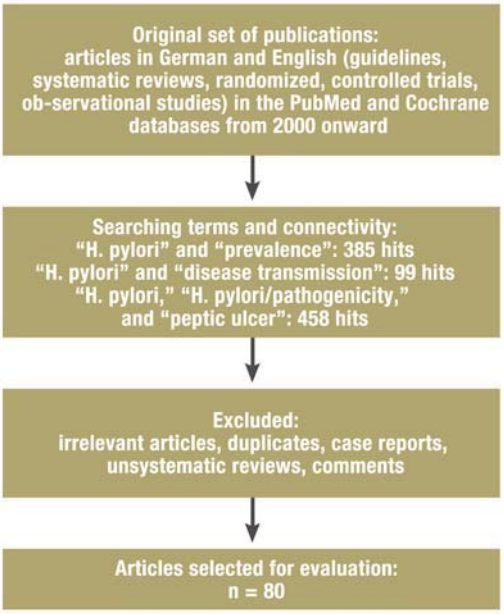
H. pylori infection can be diagnosed either directly (by demonstration of the organism or of fragments of it) or indirectly (measurement of urease activity, antibody detection). Both invasive and non-invasive diagnostic techniques can be used (A, strong consensus). All of the invasive methods are based on endoscopy and the acquisition of biopsy specimens. The various tests have high sensitivity and specificity *(Table 3)* (8, 9), but false-positive and false-negative results remain possible. The former may be due to bacterial colonization of the mouth, pharynx, or stomach, while the latter may be seen in cases of acute upper gastrointestinal bleeding, or when the bacterial colonization is of low density in the aftermath of partial gastric resection or suppressive treatment for *H. pylori*.

Criteria for reliable diagnosis

The selection of a testing procedure to demonstrate *H. pylori* infection depends on the question being asked, as well as on the indication. Whenever endoscopy is performed, a rapid urease test combined with histology is an option. This procedure involves the taking of one biopsy specimen each from the antrum and corpus of the stomach for the rapid urease test, and then of two further specimens from each of these sites for histology. It thus fulfils the requirement of two positive test results for the diagnosis of *H. pylori* infection (C, strong consensus). The only exception to this rule is duodenal ulcer, for which a single positive test result suffices for therapeutic decision-making, in view of the high prevalence of *H. pylori* in this disease. Histology has the main advantage that it not only reveals the presence of the organism, but also yields information about the distributive pattern and activity of gastritis. Culture is 100% specific, but relatively cumbersome and expensive, because the biopsy specimens must be sent to a microbiology laboratory in a special nutritive medium. Therefore, culture is usually performed only when resistance testing is needed. If the rapid urease test and the histology yield discordant results, then a urea breath test or stool antigen test for monoclonal antibodies is performed next. Serological tests are an unsuitable basis for therapeutic decision-making, as they cannot differentiate prior infections from persistent infections that require treatment.

Attention should be paid to the minimum temporal interval between any prior suppressive treatment for *H. pylori* and the performance of the test: two weeks after

FIGURE 1



Flowchart: Systematic literature search on Topic group 1, "epidemiology" (searching terms, connectivity, number of articles in the primary search, articles that were not considered for evaluation, evaluated articles)

TABLE 1

Classification of consensus strength

Strong consensus	Agreement among >95% of participants
Consensus	Agreement among 75– 95% of participants
Majority decision	Agreement among 50–75% of participants
No consensus	Agreement among <50% of participants

TABLE 2

Recommendation grade and evidence strength

Recommendation grade	Evidence strength	Comment
A	1	Systematic review (with homogeneity) of randomized controlled trials
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Exploratory cohort studies or randomized controlled trials of low quality
C	3	Systematic review (with homogeneity) of case-control studies, or individual case-control studies
	4	Case series and poor-quality case-control studies
D	5	Expert opinion, or inconsistent or non-determinative evidence from trials of any level of evidence quality

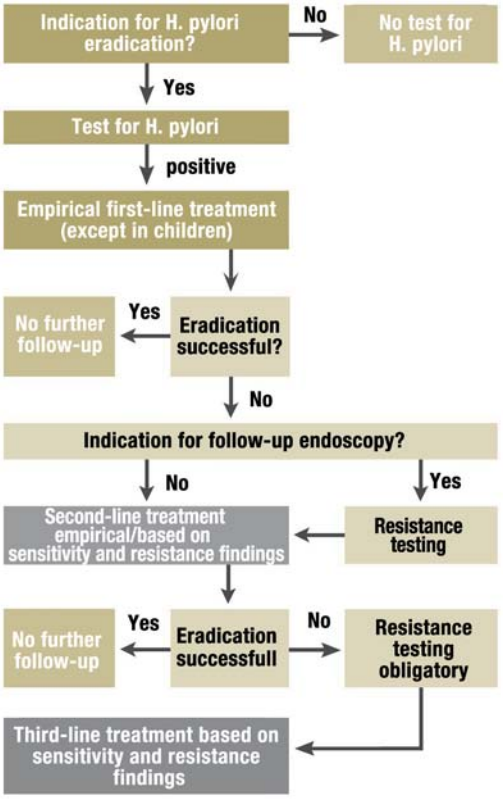
TABLE 3

Sensitivity and specificity of tests for the detection of H. pylori (8, 9)

		Sensitivity (%)	Specificity (%)
Invasive methods	Culture	70–90	100
	Histology	80–98	90–98
	Rapid urease test	90–95	90–95
	PCR	90–95	90–95
Non-invasive methods	Urea breath test	85–95	85–95
	Monoclonal antibody based stool antigen test	85–95	85–95
	Serum IgG antibody detection	70–90	70–90

Necessary steps from the diagnosis to the treatment of H. pylori infection

FIGURE 2



treatment with proton-pump inhibitors and four weeks after eradication therapy or antibiotic treatment for other indications (C, consensus). It is unclear whether H_2-receptor antagonists also lower test sensitivity.

From diagnosis to treatment

The required steps from diagnosis with the methods described above to treatment are summarized in *Figure 2*.

First, it must be determined whether a diagnostic evaluation for *H. pylori* is indicated and whether eradication therapy would be indicated in case of a positive finding (D, strong consensus). If so, the presence of infection must always be demonstrated before treatment is begun (D, consensus). Once an infection has been diagnosed, empirical first-line treatment is initiated (except in children). This is possible in Germany because of the favorable resistance situation, which permits us to expect therapeutic success in about 90% of cases. If successful eradication is confirmed after the necessary minimum interval of time between the end of treatment and the test, routine follow-up testing for *H. pylori* reinfection is not necessary (B, strong consensus). If the bacterium has not been eradicated, the course of further treatment depends on whether follow-up endoscopy is indicated. If endoscopy is performed, biopsy specimens should be taken for culture and resistance testing (B, majority agreement). This makes it possible for second-line treatment to be given in accordance with the patient's specific pattern of drug resistances and sensitivities. If endoscopy is not performed, second-line treatment is given empirically; if this also fails to eradicate the organism, then endoscopy with biopsy for culture and sensitivity testing is mandatory (B, consensus).

Treatment of H. pylori infection

The initial treatment of *H. pylori* infection should consist of triple therapy with a proton-pump inhibitor (PPI), clarithromycin, and metronidazole or amoxicillin, given for at least one week (A, strong consensus) *(Table 4)* (12). Sequential treatment (PPI and amoxicillin for five days, followed by PPI, clarithromycin, and an imidazole derivative for five days) or other types of quadruple therapy are alternative options (A, majority agreement) (20). The data on sequential treatment were, however, obtained in countries with incomparably higher rates of clarithromycin resistance and thus do not necessarily reflect the likelihood of success of this treatment in Germany. Another reason why sequential treatment cannot be generally recommended is the complex mode of administration. It is a fact of practical significance that prior reduction of gastric acidity with a PPI does not endanger the success of *H. pylori* eradication, and thus intravenous antibiotics are not necessary for patients in intensive care units who have bleeding ulcers (A, strong consensus). The rate of severe complications should be less than 5% (D, consensus), as it indeed is for the first-line protocol outlined here. Nearly all side effects are due solely to the antibiotics used.

Second-line treatment is given either in accordance with the determined pattern of antibiotic resistances and sensitivities, or else empirically *(Figure 2)*. *Figure 3* lists the eradication protocols that are available for empirical second-line treatment (21). Attention should be paid to the possible induction of antibiotic resistance and to any individual intolerances or allergies the patient may have (B, strong consensus). Moreover, accompanying measures that markedly increase the chance of success should be meticulously applied. Third-line treatment should always be initiated by a specialist on the basis of resistance testing.

Special considerations in children and adolescents

With regard to *H. pylori* infection, children and adults differ in many ways, as discussed in detail in the guideline (2). Two practically important aspects deserve special emphasis here: A "test-and-treat" strategy is inappropriate for symptomatic children and adolescents (C, consensus). Sensitivity testing of gastric biopsy specimens should always be performed before the first treatment is provided, and the particular type of eradication therapy to be used should be chosen according to the results (B, strong consensus).

Indications for eradication therapy

The indication for eradication therapy can be absolute, relative, or absent. In the guideline, the position of the recommendation along this continuum is indicated by an auxiliary verb: *H. pylori* either "must," "should," "may," or "should not" be eradicated. *Table 5* contains a summary of the indications together with the corresponding recommendation grades, consensus strengths, and special remarks. There are three major groups of conditions in which a decision about eradication therapy is needed:

- Gastroduodenal diseases
- Use of traditional non-steroidal anti-inflammatory drugs (tNSAIDs) and acetylsalicylic acid (ASA)
- Extragastric diseases.

Some special aspects of the indications listed in *Table 5* receive further comment in what follows. The most common and most evidence-based recommendation for eradication therapy is peptic ulcer. Whether the ulcer is present and florid or known from the patient's history, complicated or uncomplicated, gastric or duodenal, *H. pylori* eradication therapy should always be provided.

In functional dyspepsia, there are two fundamentally different situations that must be distinguished from each other. A "test-and-treat" strategy, i.e., the noninvasive demonstration of *H. pylori* infection followed by eradication therapy without any evaluation of the patient's dyspeptic symptoms by endoscopy, is inappropriate in principle. *H. pylori* eradication therapy can be performed, however, if other causes of dyspepsia have been ruled out by endoscopy. According to the German ELAN study, the number needed to treat (NNT) in this situation is 15 (13).

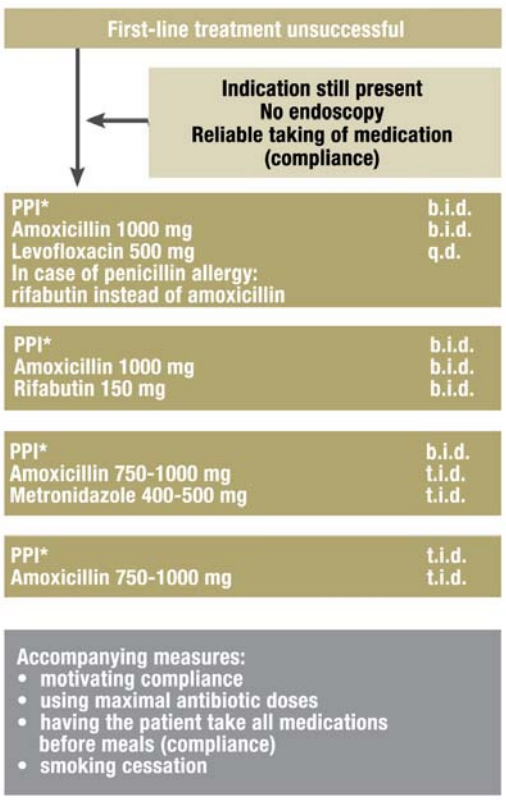
TABLE 4

Suitable therapeutic approaches to first-line treatment of H. pylori infection

Name	Days	Agents	Dosing
Italian TT	1–7	PPI*	b.i.d.
	1–7	Clarithromycin 250–500 mg	b.i.d.
	1–7	Metronidazole 400–500 mg	b.i.d.
French TT	1–7	PPI*	b.i.d.
	1–7	Clarithromycin 500 mg	b.i.d.
	1–7	Amoxicillin 1000 mg	b.i.d.
Sequential therapy	1–5	PPI*	b.i.d.
	1–5	Amoxicillin 1000 mg	b.i.d.
	6–10	PPI*	b.i.d.
	6–10	Clarithromycin 500 mg	b.i.d.
	6–10	Metronidazole 500 mg	b.i.d.
Quadruple therapy	1–7	PPI*	b.i.d.
	1–7	Clarithromycin 250–500 mg	b.i.d.
	1–7	Metronidazole 400 mg	b.i.d.
	1–7	Amoxicillin 1000 mg	b.i.d.

*Proton pump inhibitor (PPI) dose: esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg.
TT, triple therapy. Tables 1–4 from Fischbach et al.: S3 guideline on *Helicobacter pylori* and gastroduodenal ulcer disease of the German Society for Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten*, DGVS). Z Gastroenterol 2009; 47: 68–102 (with the kind permission of Georg Thieme Verlag, Stuttgart/New York.)

FIGURE 3



Options for empirical second-line treatment after failure of first-line treatment; duration of treatment, 10 days (14 days for dual treatment). *Proton-pump inhibitor (PPI) dose: esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg

TABLE 5

Indications for the eradication of H. pylori

	Absolute indication ("must be eradicated")	Relative indication ("should be eradicated")	Relative indication ("may be eradicated")	No indication ("should not be eradicated")	Rcommendation grade, consensus strength, remarks
Peptic ulcer, whether complicated or uncomplicated, current or prior	X				A (strong consensus)
Gastric MALT lymphoma, stage I/II	X				A (strong consensus)
Functional dyspepsia (diagnosis of exclusion)		X			A (strong consensus)
Functional dyspepsia (not investigated, i.e., "test and treat")				X	D (consensus)
Asymptomatic gastritis			X		A (consensus)
Ménétrier's disease			X		C (strong consensus)
Lymphocytic gastritis			X		C (later vote by e-mail poll)
Gastric carcinoma prophylaxis in persons at risk[*1]			X		C (strong consensus)
Before long-term treatment with tNSAIDs in patients with risk factors[*2]		X			A (consensus) PPI as accompanying treatment
Current long-term treatment with tNSAIDs				X	
Upper gastrointestinal bleeding under tNSAIDs			X		D (consensus) PPI obligatory in case tNSAIDs continue to be used thereafter
Before long-term treatment with ASA				X	B (consensus)
Upper gastrointestinal bleeding under ASA		X			B (strong consensus) simultaneous long-term treatment with PPI
Idiopathic thrombocytopenic purpura (ITP)			X		B (consensus)
Iron-deficiency anemia of unknown cause (after adequate diagnostic evaluation)			X		C (consensus)

[*1] Persons at risk: *H.-pylori*-positive pan- or corpus-dominant gastritis, first-degree relatives of persons with gastric carcinoma, endoscopic resection of a gastric adenoma or early carcinoma.

[*2] Risk factors: age over 65, history of ulcer, co-medication with ASA or steroids, oral anticoagulation

Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) and ASA are recognized ulcerogenic factors that affect therapeutic decision-making when patients taking them simultaneously have an *H. pylori* infection. The considerations include:

- Whether long-term treatment with these drugs (i.e., for longer than 4 weeks) is planned or is already in progress
- Whether there are any additional risk factors for gastrointestinal side effects *(Table 5)*
- Whether the patient is taking tNSAIDs, ASA, or both
- Whether these medications have already caused complications, such as upper gastrointestinal bleeding.

Treating the patient with a PPI in addition to eradicating *H. pylori* is considered to have a greater preventive effect than *H. pylori* eradication alone and is indicated ("may" or "should" be performed) in certain situations that are listed in *Table 5*.

New scientific knowledge since issuance of the guideline

The guideline contains an optional recommendation for *H. pylori* eradication for the prevention of gastric carcinoma in persons at risk. The latter category includes patients with pan- or corpus-dominant gastritis and first-degree relatives of patients with gastric carcinoma. The cancer-preventing effect of bacterial eradication is greater the earlier the treatment is provided. Once atrophy or intestinal metaplasia has developed, a point of no return may have been reached. Nonetheless, in a randomized trial in Japan, *H. pylori* eradication was also found to prevent the development of metachronic

carcinoma to a significant extent in patients who had undergone endoscopic resection of an early gastric carcinoma (odds ratio 0.353, 95% confidence interval 0.161–0.775) (24).

The guideline contains a recommendation that accompanying PPI medication should be given to patients taking ASA and clopidogrel simultaneously, because this combination has been shown to increase the risk of gastrointestinal hemorrhage. This recommendation, however, needs to be modified in the light of more recent data. Two retrospective cohort studies published in 2009 provide evidence that the combination of clopidogrel and PPI's elevates cardiovascular risk (25, e1). In view of this finding, and with the approval of the European Medicines Agency (EMEA), a "red-hand letter" (urgent safety information) was sent out, stating that "the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary." The theoretical explanation for this finding may lie in the fact that one of these two substances is activated, and the other metabolized, by the same cytochrome P450 subtype (CYP2C19). Nonetheless, two of three post-hoc analyses of data from randomized studies (e2–e5) have failed to show any negative effect of PPI's. The decision whether to use a PPI in a patient taking clopidogrel should thus be made judiciously and on the basis of the patient's individual gastrointestinal risk. A joint position statement on this issue from gastroenterologists and cardiologists would be desirable, in view of the importance of the problem and the large number of cardiac patients affected by it.

Conflict of interest statement
Prof. Fischbach has received lecture honoraria from the Abbott, Sanofi-Aventis, AstraZeneca, Nycomed, Falk, Pfizer, and Norgine companies.
Dr. Bolten has received fees for acting as a consultant, as well as lecture honoraria, from the Pfizer, MDS, and AstraZeneca companies.
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PD Dr. Hoffmann owns shares in Siemens, is a consultant for Essex, and has received lecture honoraria from the Abbott, Esai, Essex, and Falk companies.
Prof. Koletzko has received financial support for research from the Oxoid Ltd. Hampshire, AstraZeneca, and Wedel companies. She has received fees for acting as a consultant for AstraZeneca as well as lecture honoraria from the AstraZeneca and Wedel companies.

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CLINICAL PRACTICE GUIDELINE

Helicobacter Pylori and Gastroduodenal Ulcer Disease

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